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Beat-to-beat Cardiac Output inference using heart sounds

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Abstract—**Cardiac output (CO) change is the primary compensatory mechanism that responds to oxygenation demand. Its continuous monitoring has great potential for the diagnosis and management of cardiovascular diseases, both in hospital as well as in ambulatory settings. However, CO measurements are currently limited to hospital settings only. In this paper, we present an extension of the model proposed by Finkelstein for beat-to-beat CO assessment. We use a non-linear model consisting of a two-layer feed-forward artificial neural network. In addition to demographic (body surface area and age) and physiological parameters (HR), surrogates of contractility, afterload and mean arterial pressure based on systolic time intervals (STIs), estimated from echocardiography and heart sounds are used as inputs to our models. The results showed that the proposed models - with echocardiography as reference - produce better estimations of stroke volume/CO than the Finkelstein model (12.83±10.66 ml vs 7.23±6.6 ml), as well as higher correlation (0.46 vs 0.82).**

I. Introduction

CARDIAC Output (CO) is one of the main variables controlled by the autonomous nervous system to react to the physiological need of organ perfusion and oxygen delivery [1]. Continuous monitoring of CO has many applications, both in acute and long-term chronic care. In acute care, it is observed that derangements in circulation are common in major classes of illness such as sepsis, trauma and surgery [2, 3]. Detailed evaluation of the circulation is, therefore, an essential aspect to adequately perform informed decisions for routine patient management in acute settings, having significant impact on the outcome [3]. For chronic patient management, continuous CO assessment (i.e. repeated daily measurements) might enable the detection of changes in hemodynamic trends with envisioned impact on timely detection of disease progression and medication tailoring.

Throughout the years, there have been several technological advances in CO measurement. In clinical practice, one of the reference methods for CO measurement has been the pulmonary artery catheter thermodilution method, which is now declining in favor of less invasive and continuous techniques such as lithium and cold saline indicators [2]. Low invasive and non-invasive ultrasound techniques (e.g. oesophageal Doppler) are becoming standard procedures to determine CO [4], but the requirement of expensive devices and skilled operators limit their applicability to hospital environments.

The unmet need of continuous CO monitoring techniques becomes even more evident for in prolonged in-hospital patient monitoring and chronic disease management at home, where non-invasive and low intrusive measurement principles are required. Several technologies have emerged for these application scenarios, being the most explored measurement principles, bio-impedance-based techniques (e.g. the Impedance Cardiography - ICG), Pulse Counter Analysis (PCA), Pulse Wave Analysis (PWA) and systolic time intervals (STIs). However, limitations are still recognized in these techniques. For example, the reliability of the CO measurements provided by bio-impedance-based techniques was questioned in several studies [2, 5, 6]. In arterial PCA [2], the main drawbacks are related to the dependence between aortic impedance, cardiac output and aortic compliance. Furthermore, techniques based on PWA using model flow methods (e.g. Finapres®) present inaccurate estimates of CO without invasive calibration [7].

STI-based methods for CO assessment are very appealing, since there are several measurement modalities for STI estimation that are applicable in home settings [6]. The left ventricle ejection time (LVET) has long been applied clinically as a surrogate for CO. Not surprisingly, Finkelstein et al. [8] introduced a method based on LVET to measure CO.

In this paper, we evaluate Finkelstein's method using echocardiography reference measurements both in healthy and cardiovascular diseased (CVD) populations (heart failure and coronary artery disease) and propose a non-linear extension of the STI method to measure CO. To achieve our goal, a data collection study has been conducted for the extraction of pre-ejection period (PEP), LVET and stroke volume (SV) from the synchronized acquisition of phonocardiogram (PCG), electrocardiogram (ECG) and echocardiogram (ECHO).

In section II, the proposed methodologies for the assessment of SV using STIs extracted from heart sound are outlined. In section III the clinical study protocol and the validation methods are presented. The main results are presented and discussed in section IV. Finally, in section V the main conclusions of this work are presented and some directions for future work are pointed out.

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II. METHODS

Cardiac Output (CO) is, by definition, the volume of blood ejected by the heart in a certain period of time (generally L/min). It is determined by the product of the ventricular Stroke Volume (SV) and Heart Rate (HR), i.e. $CO = SV \times HR$. Ventricular SV is the difference between the ventricular end-diastolic volume (EDV) and the ventricular end-systolic volume (ESV), i.e. $SV = EDV - ESV$. There are several variables that directly and indirectly influence these volumes and, consequently, SV. Changes in ventricular inotropy (contractility) alter the rate of ventricular pressure development, thereby affecting ESV and SV [9]. For example, the decrease in inotropy (e.g. heart failure) results in the reduction of SV and in the increase of ESV. Furthermore, chronotropy (HR) is interrelated with SV with an inverse proportion [10]. An example of this mechanism is observed in excitement, which leads to the release of the hormone epinephrine, causing a constriction in the blood vessels and in turn the increase of the HR and the decrease of the SV.

The correlation between SV and STIs has long been known. Stroke Volume is determined by the preload (i.e. end-diastolic pressure) and afterload (i.e. end-systolic pressure), which is in turn significantly associated with the Systemic Vascular Resistance (SVR), i.e. the resistance to the blood flow in the arterial system. According to Boudoulas [11], changes in afterload with resulting changes in isovolumetric pressure directly alter the Pre-ejection Period (PEP). Additionally, the respiratory change in PEP was also associated to changes in preload in critically ill patients [12]. As stated by Proença et al. [13], PEP is also greatly correlated with mean arterial pressure (MAP), which in turn is affected by SV, as well as HR, SVR and central venous pressure (CVP), as shown in eq. (1). Furthermore, LVET is correlated to the obstruction to left ventricular outflow [9], and therefore directly affects SV.

$$MAP = SV \times HR \times SVR + CVP \quad (1)$$

Age is another variable that highly influences cardiac output. Alfie *et al.* [14] observed that as patients get older, cardiac output gradually decreases at the expense of SV.

Based on these physiological findings, Finkelstein *et al.* [8] proposed a linear regression model that is a combination of both demographic and hemodynamic variables, as in (2).

$$SV_{FINK} = -6.6 + 0.25 \times LVET + 40.4 \times BSA - 0.51 \times AGE - 0.62 \times HR \quad (2)$$

In this paper, we propose two non-linear models that are an extension to the model proposed by Finkelstein *et al.* [8]. Since SV is determined not only by variables such as LVET, HR, body surface area (BSA) and age, but also by other factors such as contractility, preload and afterload, we propose the inclusion of surrogates for these parameters in the following presented models.

The STIs were estimated using an algorithm proposed by Paiva et al. [15], which is based on the analysis of heart sounds. After the estimation of PEP and LVET, a contractility index (CI) was extracted, which is defined by the ratio of PEP and LVET, i.e. $CI = PEP/LVET$ (see [16]). PEP is directly applied as a surrogate of afterload and MAP.

In the first model, the same features used by Finkelstein *et al.* [8] were used as input in a non-linear model, which is described in eq. (3).

$$SV_{NLM1} = f(LVET, BSA, AGE, HR) \quad (3)$$

In the second model, a different strategy was adopted. Each of the parameters used by Finkelstein et al. [8] were used as independent inputs in the proposed model. Additionally, surrogates of contractility and afterload were also considered in this model. The second non-linear model is presented in eq. (4).

$$SV_{NLM2} = f(LVET, BSA, AGE, HR, CI, PEP) \quad (4)$$

Since the accuracy of the proposed models highly depend on the feature space domain covered during the model identification (i.e. model training in case of a neural network), we suggest the use of a combination of both linear and non-linear models in real time scenarios. In this approach, the convex hull [17] of the known feature space is previously calculated using the training data set. During beat-by-beat measurement, the location of the feature vector is calculated and the model is chosen according to its relative position regarding to the convex hull of the feature space [18], i.e. if the feature vector is located inside the convex hull, the proposed non-linear model is used; otherwise, the choice relies on the linear model proposed by Finkelstein et al. [8]. Using this approach, we aim the minimization of the possible SV estimation errors resulting from extrapolating with the model for feature vectors located outside the known feature space (i.e. the feature space used in the construction of the model).

III. EXPERIMENTAL PROTOCOL

A. Data Collection

A data collection study was conducted at "Centro Hospitalar de Coimbra" (CHC) and involved 42 volunteers. This study was authorized by the ethical committee of CHC. The population consisted of 32 male and 10 female volunteers from which 31 subjects present no condition (healthy subjects) and 11 subjects present various cardiovascular diseases (CVD subjects). The data acquisition protocol of the data acquisition was conducted by an authorized medical specialist and consisted of a synchronous acquisition of both Echocardiography (Doppler mode) and PCG (Left sternum border and apex positions) in a relaxed, quiet and warm (ap. 22º C) environment. All volunteers were placed in supine position during the acquisitions.

The biometric characteristics of the studied population are described as follows (mean ± standard deviation):

Healthy subjects:

- Age: 29.72 ± 8.54 years
- BMI: 24.48 ± 2.41 Kg/m^2

CVD subjects:

- Age: 56 ± 17.86 years
- BMI: 24.60 ± 3.73 Kg/m^2

The echocardiographic data was annotated by a clinical expert [19] who extracted the parameters PEP, LVET and SV necessary for the evaluation of the proposed methodologies. The algorithm to estimate PEP and LVET using heart sounds is described in detail in [18].

The database is composed by 968 annotated beats, of which 789 correspond to healthy subjects and 179 to CVD subjects.

B. Model identification and validation

An Artificial Neural Network (ANN) has been adopted for the evaluation of the proposed models. The ANN consists of a two-layer feed-forward network, with 10 sigmoid hidden neurons and two linear neurons in the output layer. In the training step, the Levenberg-Marquardt backpropagation algorithm was used.

The proposed models were validated using a repeated random sub-sampling validation scheme. In this validation scheme, the dataset was randomly split into 10 subsets of training and validation data, with relative proportion of 60% and 40%, respectively. The proportion between training and validation data was kept for healthy and CVD subjects (i.e. the training data is composed by 60% of the healthy subjects beats and 60% of the CVD subjects beats, while the validation data is composed by 40% of the healthy subjects beats and 40% of the CVD subjects beats). This process of validation was repeated 20 times.

IV. Results and Discussion

The results achieved by the proposed methods are summarized in TABLE 1 and TABLE 2, focusing on the analysis of the SV estimation performance for each model: 1) the Finkelstein model (LM_{FINK}); 2) the 1st non-linear model (NLM_1) described in equation (3); and 3) the 2nd non-linear model (NLM_2) described in equation (4). For comparison purposes, the results of the intermediate models between NLM_1 and NLM_2 (i.e. NLM_1 considering PEP and NLM_1 considering CI) and the results of the models considering the reference features assessed from echocardiography (TABLE 1) are also presented. All models were tested with the global test dataset (Global) composed by 40% of the beats of the healthy and CVD subjects, and using the two aforementioned test subsets corresponding to healthy volunteers (Healthy) and volunteers with cardiovascular diseases (CVD). For performance comparison, three approaches were followed: (i) the first one was the absolute error measurement statistics with respect to the gold standard provided by echocardiography. (ii) The second utilized the method proposed by Bland and Altman (1986). (iii) Finally, the third method was least-squares linear regression analysis and the computation of correlation coefficient (r). Error distributions were tested for gaussianity using the Kolmogorov–Smirnov test. Accordingly, statistical analysis was performed using the paired Student test and the two-sided Wilcoxon signed rank test. Correlations were calculated using Pearson and Spearman's correlations, respectively.

The estimation errors were calculated by subtracting the measured parameter (x) to the reference parameter in ECHO (x_{ECHO}), i.e. $x - x_{ECHO}$. In the presented tables, the abbreviation "Error" stands for the error between measured and reference values ($x - x_{ECHO}$), while "Abs. Error" concerns to the absolute estimation error ($|x - x_{ECHO}|$). The abbreviation "Abs. Error (%)" stands for the percentage of absolute estimation error, i.e. $|x - x_{ECHO}|/\overline{x_{ECHO}}$. The results shown correspond to the ANNs that presented the absolute estimation errors closer to the average over the splitting of the datasets, hence minimizing overfitting. Furthermore, the presented results were extracted based on the evaluation of the testing subsets.

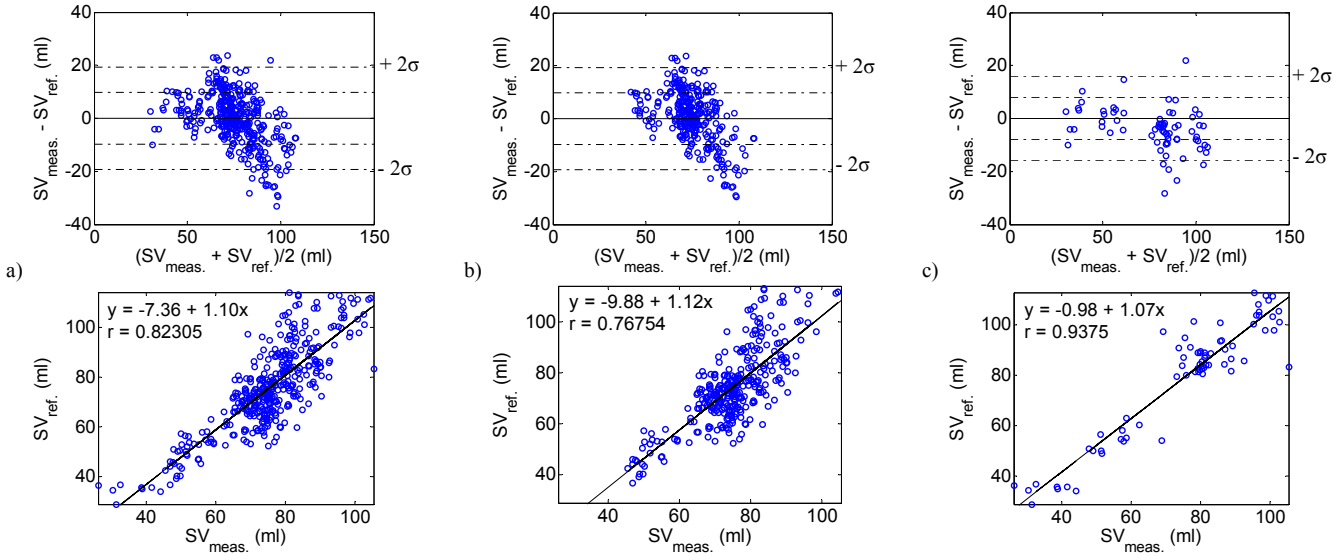

Fig. 1. Blant-Altman (top) and regression plots (bottom) for SV extracted from echocardiography (SV_{REF}) and SV estimated by model NLM_2 ($SV_{meas.}$) using a) global; b) healthy; and c) CVD datasets.

TABLE 1
STROKE VOLUME ESTIMATION RESULTS BASED ON REFERENCE PARAMETERS FROM ECHOCARDIOGRAPHY (REPEATED RANDOM SUB-SAMPLING VALIDATION)

Dataset Model	Error (ml) Avg ± std	Abs. Error (ml) Avg ± std	Abs. Error (%) Avg ± std	*r*
LM_{FINK}				
Global	00.99±15.32	12.04±09.50	16±13	0.41*
Healthy	04.89±12.88	10.78±08.57	15±12	0.51*
CVD	-16.13±13.32	17.55±11.36	22±14	0.70*
NLM_1				
Global	-00.42±09.49	06.95±06.46	09±09	0.80*
Healthy	00.81±09.14	06.87±06.07	09±08	0.77*
CVD	-05.81±09.15	07.30±07.99	09±10	0.79*
NLM_1+PEP				
Global	-00.42±08.85	06.66±05.83	09±08	0.84*
Healthy	00.18±07.81	06.28±04.64	08±06	0.81*
CVD	-03.02±12.15	08.37±09.27	11±12	0.88*
NLM_1+CI				
Global	0.11±08.56	06.63±05.41	09±07	0.81*
Healthy	0.88±08.71	06.91±05.36	09±07	0.73*
CVD	-3.27±07.00	05.40±05.50	07±07	0.94*
NLM_2				
Global	-00.79±08.87	06.72±05.84	09±08	0.85*
Healthy	-01.04±09.03	06.86±05.94	09±08	0.80*
CVD	00.30±08.14	06.07±05.39	08±07	0.94

* Estimated values using Spearman's correlation.

TABLE 1 presents the results achieved for SV measurement using the linear and non-linear models based on the STI and CI measurements extracted from the echocardiography. As can be observed, for all three assessment contexts (i.e. global, healthy and CVD data sets), the proposed non-linear models present better results than the model proposed by Finkelstein *et al.* [8], being NLM_1+CI the model that achieves lower abs. estimation error (global dataset: 6.63±5.41 ml). From the demographic context point of view, one observes that the LM_{FINK} model presents worst estimations of SV for CVD volunteers than for healthy volunteers (17.55±11.36 ml vs 10.78±8.57 ml, respectively). Contrarily, the non-linear models present better abs. estimation error for CVD volunteers than for healthy volunteers (e.g. NLM_2: 6.07±5.39 ml vs 6.86±5.94 ml, respectively), with exception to NLM_1 and NLM_1+PEP. A reduced percentage of absolute estimation error is observed for the presented models, being the LM_{FINK} the model that presents worst results (global dataset: 16%), almost twofold the percentage of estimation error for the non-linear models (global dataset: 9%). This discrepancy becomes more accentuated when analyzing the CVD dataset, where a threefold increase is observed from non-linear models (CVD dataset: 7-11%) to model LM_{FINK} (CVD dataset: 22%). The range of SV values assessed from echocardiography was 28.84-118.83 ml.

From TABLE 1, it is also observed that the correlation coefficients increase from model LM_{FINK} to non-linear models in each of the three contexts under analysis. Regarding the comparative analysis between contexts, we verified that correlation values (*r*) increase from healthy to CVD volunteers in all models. Furthermore, the close relationship between the reference and measured SV (model NLM_2) can be verified by the Blant-Altman and regression plots, presented in Fig. 1: a) global dataset; b) healthy dataset; and c) CVD dataset.

Comparing the proposed non-linear models, it is possible to observe that the inclusion surrogates of contractility and afterload, i.e. CI and PEP, resulted in improved abs. estimation errors, being NLM_1+CI the model that achieved the best results (global dataset: 6.63±5.41 ml), against the NLM_1 model (global dataset: 6.95±6.46 ml). Similarly, the inclusion of PEP and CI also resulted in enhancements on the correlation coefficients, where an increase was observed from NLM_1 (global dataset: 0.80) to NLM_2 (global dataset: 0.85).

Contrarily to the aforementioned observations, in TABLE 2 it is observed that the inclusion of the features PEP and CI extracted from heart sounds did not produce significant enhancements in the assessment of SV, both in abs. estimation error and correlation coefficients. Exceptions were seen in the models NLM_1+CI (CVD dataset: 05.90±05.84 ml) and NLM_1+PEP (healthy dataset: 0.77).

The obtained results suggest that our non-linear models achieve better performance than the model proposed by Finkelstein *et al.* [8]. In addition, SV measurement benefits from the inclusion of surrogates of afterload and contractility as long as these surrogates are measured with low uncertainty (as in echocardiography). The measurement of PEP (healthy - abs. error: 7.1±5.6 ms / r: 0.53; CVD - abs. error: 11.9±8.8 ms / r: 0.70) and LVET (healthy - abs. error: 11.2±9.3 ms / r: 0.87; CVD - abs. error: 18.0±17.4 ms / r: 0.83) derived from heart sound exhibits higher uncertainty [6] and eliminates the gained advantage to serve as surrogate of contractility. Under these circumstances, it is observed

TABLE 2
STROKE VOLUME ESTIMATION RESULTS BASED ON MEASURED PARAMETERS FROM HEART SOUNDS (REPEATED RANDOM SUB-SAMPLING VALIDATION)

Dataset Model	Error (ml) Avg ± std	Abs. Error (ml) Avg ± std	Abs. Error (%) Avg ± std	*r*
LM_{FINK}				
Global	-01.21±16.65	12.83±10.66	17±14	0.46*
Healthy	02.45±13.52	10.92±08.31	15±11	0.50*
CVD	-17.27±19.48	21.22±15.01	27±19	0.60*
NLM_1				
Global	-00.06±09.80	07.23±06.61	10±09	0.79*
Healthy	00.51±10.14	07.43±06.91	10±09	0.74*
CVD	-02.58±07.71	06.34±05.05	08±06	0.94
NLM_1+PEP				
Global	00.92±10.69	07.42±07.75	10±10	0.82*
Healthy	01.32±10.57	07.48±07.58	10±10	0.77*
CVD	-00.84±11.09	07.14±08.49	09±11	0.86
NLM_1+CI				
Global	-00.25±09.98	07.52±06.55	10±09	0.77*
Healthy	00.08±10.33	07.88±06.66	11±09	0.66*
CVD	-01.71±08.15	05.90±05.84	08±08	0.79*
NLM_2				
Global	-00.55±10.05	07.59±06.61	10±09	0.77*
Healthy	00.22±10.32	07.77±06.78	10±09	0.70*
CVD	-03.94±08.03	06.80±05.78	09±07	0.94

* Estimated values using Spearman's correlation.

that the inclusion of the afterload surrogate improves the SV estimate. However, the inclusion of CI degrades the measurement. The surrogate of contractility (CI) is subject to greater estimation errors resulting from the uncertainty in the estimation of PEP and LVET, which can be observed in model NLM_1+CI (TABLE 2).

In line of the primary objective of this study, we found that the non-linear models were able to achieve better SV estimates for CVD subjects. Furthermore, the high correlation coefficients between SV_{NLM2} and SV_{ECHO} show that the non-linear models are able to follow closely SV trends. However, more data have to be acquired to validate these results, since the CVD dataset was substantially smaller than the healthy subjects' dataset (app. 1/4).

V. Conclusions and Future Work

In the current paper, we proposed and analyzed non-linear extensions to the Finkelstein linear model, for the assessment of Stroke Volume. These models explore known correlations between cardiac output and several demographic and physiological variables that can be assessed using non-invasive techniques. In the proposed extensions, systolic time intervals as surrogates for afterload and inotropy have been integrated and have shown to significantly improve Stroke Volume measurement quality. The proposed models were tested in 42 subjects (31 healthy subjects and 11 subjects with cardiovascular diseases). The percentage of estimation error of the proposed models (app. 10%) and correlation (0.82) in comparison to the Finkelstein model (17%; correlation = 0.46) is substantially below the clinically accepted error of 30% [20]. This reveals that our approach is promising for CO monitoring of both healthy and cardiovascular diseased subjects.

Future work will focus on the extension of the proposed models to include other surrogates that determine SV. For example, peripheral resistance is known to affect afterload, ΔPEP has been associated with preload changes, while respiration contributes to high frequency changes in left ventricular function, and therefore SV. Furthermore, we intend to evaluate the weight of each variable in the proposed models output, using a feature selection technique (e.g. NMIFS). Using this kind of techniques, one is able to identify redundancy between features and consequently ignore features that do not contribute to the desired output. Furthermore, the weight of each feature can be changed depending on the demographical and physiological context under study. Other modeling approaches will also be considered as well. We will investigate the use of smooth functions to reduce discontinuities between regions inside and outside the convex hull. Another direction of further research might be the extraction of human interpretable information by using techniques such as fuzzy neural networks.

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